# Methemoglobinemia

A 16-year-old boy is seen in the emergency department after he had collapsed after a dental extraction in which prilocaine hydrochloride 3% was used as topical anesthesia. His mother tells the emergency physician that he felt unwell after the procedure and gradually became more and more drowsy. The patient is deeply cyanosed despite a good respiratory effort, a clear airway, and bilateral breath sounds. Although he initially responds to vocal commands, his level of consciousness soon deteriorates. Oxygen saturation is 60% with the patient breathing room air. An endotracheal tube is introduced and assisted ventilation started, but this does not improve his cyanosis or level of consciousness.

The attending physician is alert to the possible diagnosis of methemoglobinemia because the patient is cyanosed, the cyanosis is unresponsive to ventilation, there is no prior history of respiratory problems, and the patient had been exposed to a topical anesthetic that is known to cause methemoglobinemia.

A blood specimen is drawn and test results confirm the diagnosis.

## Summary points

- Severe methemoglobinemia is a medical emergency, requiring prompt recognition and appropriate treatment
- A good history and high level of suspicion are required to make the diagnosis
- Exposure to medication is the most common cause of methemoglobinemia
- For methemoglobinemia due to drug exposure, traditional first-line therapy consists of the infusion of methylene blue

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## METHODS

Information on methemoglobinemia was obtained through a literature search using MEDLINE and the following key words: *methemoglobinemia, sulfhemoglobinemia, cyanosis,* and *methylene blue.*

## WHAT IS METHEMOGLOBINEMIA?

Methemoglobinemia is a condition characterized by increased quantities of hemoglobin in which the iron of heme is oxidized to the ferric ($Fe^{3+}$) form. Methemoglobin is useless as an oxygen carrier and thus causes a varying degree of cyanosis.

## WHAT ARE THE POSSIBLE CAUSES?

The condition may arise as a result of a genetic defect in red blood cell metabolism or hemoglobin structure, or it may be acquired following exposure to various oxidant drugs or toxins.

### Genetic defect

Hereditary methemoglobinemia is a rare recessively inherited disorder due to deficiency of an enzyme, called reduced nicotinamide adenine dinucleotide (NADH) cytochrome $b_5$ reductase. Normal erythrocytes are well endowed with a system to convert useless methemoglobin to functional hemoglobin. The major mechanism for this reductive capacity resides in the soluble NADH cytochrome $b_5$ reductase. The gene regulating the synthesis of cytochrome $b_5$ reductase has been localized to chromosome 22q13qter, and a number of mutations have been identified.[1,2] Hereditary methemoglobinemia due to NADH cytochrome $b_5$ reductase deficiency is classified into 2 types—erythrocyte (type I) and generalized (type II).

In the type I form, the soluble form of the enzyme is deficient only in erythrocytes, and cyanosis is the only symptom.[3] Type II hereditary methemoglobinemia is due to deficiency of the membrane-bound form of the enzyme, which is located in the outer mitochondrial membrane and the endoplasmic reticulum of somatic cells. Type II hereditary methemoglobinemia is a rare disease characterized by deficiency of the enzyme in all tissues and manifesting with severe developmental abnormalities, severe mental retardation, and neurologic impairment, which often lead to premature death.[4] Heterozygotes with NADH cytochrome $b_5$ reductase deficiency do not usu-

ally manifest signs of methemoglobinemia. However, under the stress of oxidant drugs, severe cyanosis may develop because of methemoglobinemia. Neurologic abnormalities do not respond to methylene blue therapy.

There are several abnormal hemoglobin variants associated with genetic methemoglobinemia, and these are designated hemoglobin M. In most of the hemoglobin M, tyrosine has been substituted for either the proximal or the distal histidine. This results in reduced capacity of the enzymatic machinery of the erythrocyte to efficiently reduce the iron to the divalent form and thus predisposes to methemoglobinemia. These hemoglobin variants are associated with cyanosis, which is present from early life. In the case of the α-chain variants, it is present from birth, whereas the β-chain hemoglobin variants produce cyanosis only after the first few months of life as adult hemoglobin synthesis becomes established. This disorder is inherited in an autosomal dominant pattern.

## Exposure to drugs or toxins

The most common cause of methemoglobinemia, as in this clinical case, is ingestion of or exposure of skin or mucous membranes to oxidizing agents (see box). Some of these oxidize hemoglobin directly to form methemoglobin; others do it indirectly by reducing free oxygen to the free radical $O_2^-$, which in turn oxidizes hemoglobin to methemoglobin. Outbreaks of methemoglobinemia have occurred due to nitrite poisoning from water contamination.[5]

Large amounts of nitric oxide are released in patients with sepsis. Nitric oxide is converted to methemoglobin and nitrate. It has been reported that methemoglobin levels are significantly higher in patients with sepsis than in nonseptic patients.[6]

Methemoglobinemia has been reported in young infants (<6 months) in whom severe metabolic acidosis develops from diarrhea and dehydration.[7] Young infants may be particularly susceptible to this complication because of their low stomach acid production, large number of nitrite-reducing bacteria, and the relatively easy oxidation of fetal hemoglobin. Small infants have lower erythrocyte levels of cytochrome *b* reductase.[8] Higher intestinal pH of infants may promote the growth of gram-negative organisms that convert dietary nitrates to nitrites.

Methemoglobinemia has been reported in diarrhea induced by hypersensitivity to cow's milk proteins.[9] It has also been reported in association with renal tubular acidosis.[10]

This patient has no family history of the disease, which makes genetic causes unlikely. Structural alteration of α- or β-globin chains of hemoglobin

**Drugs or toxins that can cause methemoglobinemia***

- Acetanilid
- Alloxan
- Aniline
- Arsine
- Benzene derivatives
- Benzocaine
- Bivalent copper
- Bismuth subnitrate
- Bupivacaine hydrochloride
- Chlorates
- Chloroquine
- Chromates
- Clofazimine
- Dapsone
- Dimethyl sulfoxide
- Dinitrophenol
- Exhaust fumes
- Ferricyanide
- Flutamide
- Hydroxylamine
- Lidocaine hydrochloride
- Metoclopramide hydrochloride
- Methylene blue
- Naphthalene
- Nitrates
- Nitric oxide
- Nitrites
- Nitrofuran
- Nitroglycerin
- Sodium nitroprusside
- Paraquat
- Phenacetin
- Phenazopyridine hydrochloride
- Phenol
- Phenytoin
- Prilocaine hydrochloride
- Primaquine phosphate
- Rifampin
- Silver nitrate
- Sodium valproate
- Smoke inhalation
- Sulfasalazine
- Sulfonamides
- Trinitrotoluene

*Certain drugs are more likely to cause methemoglobinemia than others. These are dapsone, local anesthetics, phenacetin, and antimalarial drugs. Screening everybody for methemoglobinemia before exposing them to these drugs is impractical because of the rarity of the condition and because a growing number of drugs are implicated in its causation.

would have presented early in infancy, and type I hereditary methemoglobinemia can reasonably be excluded on the basis that chronic low-grade cyanosis is the only symptom. The absence of neurologic signs excludes type II hereditary methemoglobinemia. The most likely cause of methemoglobinemia, therefore, is acquired by exposure to prilocaine hydrochloride.

## WHAT ARE THE OTHER CLINICAL SIGNS AND COMPLICATIONS?

Methemoglobinemia may be acute or chronic. The physiologic level of methemoglobin in the blood is 0% to 2%.[2] Methemoglobin concentrations of 10% to 20% are tolerated well, but levels above this are often associated with symptoms. Levels above 70% may cause death. Symptoms also depend on the rapidity of its formation. Many patients with lifelong methemoglobinemia are asymptomatic, but patients exposed to drugs and toxins who abruptly develop the same levels of methemoglobinemia may be severely symptomatic.

Small infants with methemoglobinemia present with cyanosis that fails to respond to supplemental oxygen. Cyanosis in those with congenital methemoglobinemia usually appears shortly after birth. Dyspnea, nausea, and tachycardia occur at methemoglobin levels of 30% or more. Lethargy, stupor, and deteriorating consciousness occur as methemoglobin levels approach 55%. Higher levels may cause cardiac arrhythmias and circulatory failure. Hemolytic anemia may follow drug-induced methemoglobinemia, especially with exposure to dapsone, sulfasalazine, or phenacetin. The anemia is characterized by Heinz bodies (precipitated hemoglobin or globin subunits due to denaturation of hemoglobin in erythrocytes) and fragmented red blood cells. Occasionally acute intravascular hemolysis can lead to renal failure. Hemolytic anemia with jaundice may also be a feature of hemoglobin $M_{Saskatoon}$ and hemoglobin $M_{Hyde\ Park}$—abnormal hemoglobin variants associated with genetic methemoglobinemia and identified by where they were discovered.

The patient is monitored for evidence of intravascular hemolysis and acute renal failure. His urine output, blood cell count, and urea and electrolyte levels are monitored closely. Any evidence of hemolysis should alert the physician so that appropriate treatment can be instituted.

## WHAT IS THE DIFFERENTIAL DIAGNOSIS?

The differential diagnosis of methemoglobinemia in small infants includes cyanotic congenital heart disease, particularly when right to left shunting is present. Children with cyanotic congenital heart disease who receive supplemental oxygen have a low partial pressure of oxygen and a low calculated oxygen saturation, but children with methemoglobinemia have a high partial pressure of oxygen despite cyanosis and normal calculated oxygen saturation.

Methemoglobinemia in older children should be distinguished from sulfhemoglobinemia. Sulfhemoglobinemia refers to the incorporation of a sulfur molecule into the heme moiety. Most drugs, particularly sulfonamides and phenacetin, that produce methemoglobinemia can also cause sulfhemoglobinemia, although this condition is less common than methemoglobinemia.[11] Symptoms tend to be milder than in patients with methemoglobinemia. The diagnosis is confirmed by elevated levels of sulfhemoglobin by either spectrophotometry or gas chromatography-mass spectrometry. Sulfhemoglobinemia does not respond to methylene blue, and the treatment is supportive.[12] In severe cases, exchange transfusion may be useful.

The potassium cyanide test can distinguish between methemoglobin and sulfhemoglobin. After the addition of a few drops of potassium cyanide, methemoglobin turns bright red, but sulfhemoglobin remains dark brown. This is due to the binding of methemoglobin to cyanide, forming cyanomethemoglobin, which is bright red in color. Sulfhemoglobin, on the other hand, is inert and does not bind cyanide.[13]

A family history is usually helpful in differentiating methemoglobinemia due to NADH cytochrome $b_5$ reductase deficiency from hemoglobin M disease. Cyanosis in successive generations suggests the presence of hemoglobin M; normal parents but possibly affected siblings implies the presence of NADH cytochrome $b_5$ reductase deficiency.

## HOW DO YOU CONFIRM THE DIAGNOSIS?

Blood containing high concentrations of methemoglobin appears chocolate brown. Subjects with methemoglobinemia may have normal partial pressures of oxygen, despite life-threatening methemoglobinemia. The oxygen saturation values, measured by a pulse oximeter, are falsely elevated.

In methemoglobinemia due to drug exposure, an elevated level of methemoglobin is found, but the activity of NADH cytochrome $b_5$ reductase is normal. In hereditary type II methemoglobinemia, the enzyme's activity is less than 20% of normal. Hemoglobin M may be differentiated from methemoglobin formed from hemoglobin A by its absorption spectrum in the range of 450 to 750 nm. Electrophoresis at pH 7.1 is most useful for the separation of hemoglobin M.[14]

## WHAT TREATMENT WORKS?

The course of hereditary methemoglobinemia type I is benign, but these patients should not be administered oxidant drugs. Treatment may be required for cosmetic reasons or for an inadvertent use of oxidant drugs. Ascorbic acid, 300 to 600 mg orally daily divided into 3 or 4 doses, is helpful.[15]

For methemoglobinemia due to drug exposure, traditional first-line therapy consists of an infusion of methylene blue, whose action depends on the availability of reduced nicotinamide adenine nucleotide phosphate (NADPH) within the red blood cells. After an acute exposure to an oxidizing agent, treatment should be considered when the methemoglobin is 30% in an asymptomatic patient and 20% in a symptomatic patient.[16] Patients with anemia or cardiorespiratory problems should be treated at lower levels of methemoglobin. Methemoglobinemia due to hemoglobin M does not respond to ascorbic acid or methylene blue.

Dextrose should be given[17] because the major source of NADH in the red blood cells is the catabolism of sugar through glycolysis. Dextrose is also necessary to form NADPH through the hexose monophosphate shunt, which is necessary for methylene blue to be effective.

Methylene blue is an oxidant; its metabolic product leukomethylene blue is the reducing agent. Therefore, large doses of methylene blue may result in higher levels of methylene blue rather than the leukomethylene blue, which will result in hemolysis and, paradoxically, methemoglobinemia in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency.[18] Patients with G6PD deficiency also may not produce sufficient NADPH to reduce methylene blue to leukomethylene blue; thus, methylene blue therapy may be ineffective in these patients.[18]

Some drugs, such as dapsone, benzocaine, and aniline, produce a rebound methemoglobinemia, in which methemoglobin levels increase 4 to 12 hours after successful methylene blue therapy.[19]

*N*-Acetylcysteine, cimetidine, and ketoconazole are experimental therapies in the treatment of methemoglobinemia that have shown some promising results.[20-22] Exchange transfusion is reserved for patients in whom methylene blue therapy is ineffective.

The patient is treated with intravenous methylene blue and dextrose infusion, with a good response. His cyanosis and blood oxygenation improve, as does his consciousness level. His urine output is monitored, and a close eye is kept on his biochemistry. Blood tests are repeated after 24 hours for evidence of hemolysis and rebound methemoglobinemia. His G6PD status is ascertained and found to be normal. He does not show any evidence of hemolysis or renal impairment and makes a complete recovery.


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